REMARKS

Claims 1-13 are currently pending in the application. Claims 1-3 and 6-13 are in independent form.

Claims 1-8 stand rejected under 35 U.S.C. § 102(b) as being anticipated by the Moskowitz patent. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by the Moskowitz patent, as applied to the claims is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

In Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986) it was stated: "For prior art to anticipate under §102 it has to meet every element of the claimed invention."

In Richardson v. Suzuki Motor Co., Ltd., 868 F.2d 1226, 9 U.S.P.Q.2d 1913 (Fed. Cir. 1989) it was stated: "Every element of the claimed invention must be literally present, arranged as in the claim."

The Office Action states that the Moskowitz patent teaches a method of treating strokes and the resulting neurological damage by administering nitric oxide releasing compounds. The therapeutic target of the Moskowitz approach is the reduction of cerebral infarction (i.e. volume of dead brain tissue) after ischemic stroke that is stroke caused by a lack of blood flow to the brain. Moskowitz seeks to increase blood flow to the brain to limit volume of infarction. In other words, the patent discloses treating injured brain in an attempt to salvage brain tissue. The treatment disclosed in the Moskowitz patent is limited to times early after onset of ischemic stroke when blood flow increase can reduce the volume of blood flowing to the damaged tissue. In the Moskowitz patent, there is disclosed that the reduction of the infarction is mediated by administration of a substrate for NO before or early (within the first 1-2 hours) after stroke. The substrate is given from 16 hours before stroke to 2 hours after stroke. This enhances blood flow to the brain and thereby counteracts some of the loss of blood flow initiated by the stroke. The Moskowitz patent states in column 1 line 31 that, "the nervous system lacks the ability to regenerate," in column 1 lines 40- 44, "the ultimate size of the infarct which forms the basis of medical therapy is the extent of vascular

support." Thus, according to the Moskowitz patent, the intervention must be designed to improve blood flow and thereby to reduce the ischemic lesion, because when the lesion is complete, the lesion cannot be reduced by treatment there is no benefit.

The Moskowitz patent also discloses that the brain cannot regenerate. The data presented in the Moskowitz patent only relate to treatment of a model of ischemic stroke with a substrate of NO. All data presented by Moskowitz show a reduction of volume of cerebral infarction, dilation of blood vessels, and, as noted in column 3 line 18, the approach of the Moskowitz patent is to "limit the extent of stroke-associated infarct." The patent discloses that treatment should preferably begin shortly after the initiation of stroke and preferably at any point in time prior to the completion of the infarction process. There is disclosed that "treatment may be initiated, however, at any point in time prior to the completion of the infarction process." The disclosure also provides that "in certain instances, the methods of the invention may be used to treat a patient after the completion of a stroke episode." There is no disclosure of what those "instances" are or how they relate to treatment and thus, the disclosure does not enable one of skill in the art to ascertain the possibility that any beneficial effects are afforded a patient who has the NO compound administered post-stroke. Further, there is no disclosure that treatment at any point subsequent to the completion of the stroke would function in the desired manner. It is commonly known to those of skill in the art that there is a distinct period of time in which the damage occurring from a stroke can be mediated. Subsequent to this time period, it was believed that treatment was futile. Further, the Moskowitz patent and all other prior art disclosures disclose methods for limiting the infarction process or increasing the blood flow to the areas of the brain that were damaged by stroke. There is no disclosure for the regeneration of neurons as is disclosed in the presently pending independent claims.

In contradistinction, the presently pending independent claims claim therapeutic compounds including PDE5 inhibitors and related compounds, for inducing brain remodeling and restoring neurological function, completely independent of the effect of NO donors on the volume of infarction. As disclosed throughout the currently pending patent application and specifically claimed, the functional benefit is derived from treatment under conditions in which the volume of brain damage is unaltered by the

treatment. Further, the claimed methods are used to treat and remodel viable brain. The method activates endogenous restorative mechanisms within the non-injured tissue, so as to compensate for the damage, and thereby to enhance neurological function. The therapy is designed to be given days and weeks after the injury, and the neurogenesis is totally independent of any affect of treatment of the lesion. The claimed method is specifically delayed until the completion of infarction, and can even be administered 24 or more hours after stroke. The method and compound of the presently pending independent claims claim inducing brain remodeling an event that is independent of the reduction of the volume of cerebral infarction. There is no connection or association of reduction of volume of cerebral infarction and with the production of new brain cells. There is no requirement of the presence of a NO donor to induce brain remodeling and functional benefit.

The Office Action has maintained that Applicants' definition of promoting neurogenesis includes proliferation of parenchymal cells and as such, is much broader than originally suggested. However, when read more specifically, the definition of promoting neurogenesis is defined as "new neuronal growth or enhanced growth of existing neurons, as well as growth and proliferation of parenchymal cells and cells that promote tissue plasticity." The neurogenesis occurs as stated on page 7, lines 5-15 due to increased levels of cGMP resulting from the administration of the NO donor. The increased amount of cGMP increases the number of progenitor cells and the number of Tuj1 immunoreactive cells in the ischemic brain, thus enhancing the functional recovery after stroke. The recovery includes the increase of parenchymal cells as a result of the proliferation of new neurons, therefore, the parachymal cells are increased as a result of the neurogenesis. cGMP functions to increase neurons because the NO activates glutamate receptors and the glutamate receptors promote long-term potentiation and therefore, induce regeneration of neurons. Additionally, the methodology disclosed in the Moskowitz patent does not initiate neurogenesis. In fact, the Moskowitz patent discloses that neurons cannot regenerate. It is actually contrary to the common knowledge of those in skill in the art to have administered any compounds after the completion of the stroke. Instead, it was believed by those of skill in the art that upon completion of the stroke, an individual was no longer able to be

treated and must instead learn to survive with the results of the stroke. Since the Moskowitz patent does not disclose or suggest the method and compound of the presently pending independent claims, the claims are patentable over the Moskowitz patent, and reconsideration of the rejection is respectfully requested.

Claims 1-8 stand rejected under 35 U.S.C. § 102(b) as being anticipated by the Liao patent. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by the Liao patent, as applied to the claims is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

The Office Action states that the Liao patent teaches upregulation of endothelial cell nitric oxide synthase expression by administration of HMG CoA reductase inhibitors. The Liao patent discloses that endothelial cell nitric oxide synthase can be upregulated by agents that disrupt cytoskeletal organization. As specified in column 5 lines 9-10, "the inventors provide a method for reducing brain injury resulting from stroke." As stated in column 8, lines 60-68, the method of the Liao patent invention is designed to reduce volume of infarction. The Liao patent specifically discloses that, "a functional test for measuring neurological deficits provided further evidence of reduction in brain injury in the treated animals versus controls." Thus, the Liao patent specifically discloses to a reduction of infarct. The Liao patent thus establishes a connection between neurological defects and volume of infarction. In contradistinction, the presently claimed invention discloses and claims a method of treating neurological damage independent of the volume of infarction, as these are two unrelated conditions.

Specifically, the presently pending independent claims claim a compound and method for treating neurological deficits that is independent of reduction of cerebral infarct volume. There is no relationship between volume of injury and brain regeneration. There is no disclosure in the Liao patent that suggests a relationship between NO donors, PDE5 inhibitors and the production of new neurons. The statement on page 8 of the Office Action that "the general promotion of neurogenesis must inevitably occur," stands in contradiction to the assertion by Liao of a direct relationship between reduction brain injury and reduction of neurological defects. Liao implies that reduction of neurological deficits only occurs within the context of reduction

of volume of cerebral infarction, in direct conflict with the presently pending independent claims. Reduction of brain injury is not related to neurogenesis. The Liao patent does not provide any data or evidence that cognitive or functional deficits are reduced with treatment. All of the examples provided by the Liao patent involve the administration of a statin agent to the mouse 14 days prior to the induction of stroke (Examples 15,17,18). There were no measurements of neurological function. Liao only shows that the volume of cerebral infarction is reduced when treatment with a statin is initiated 2 weeks prior to stroke and there is no support or suggestion in the Liao patent that the treatment could either occur at a later time period or that the treatment would function to create neurogenesis. Since the Liao patent does not disclose or suggest the method and compound of the presently pending independent claims, the claims are patentable over the Liao patent, and reconsideration of the rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above. The prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

It is respectfully requested that the present amendment be entered in order to place the application in condition for allowance or at least in better condition for appeal. The application is placed in condition for allowance as it addresses and resolves each and every issue that remains pending. Claims have also been amended to clearly distinguish over the prior art. The application is made at least in better condition for appeal as the amendment removes many issues thereby simplifying the issues on appeal. Further, the claims have been amended to more specifically define the invention while raising no new issues that would require any further searching. Rather, the amendments have been made in view of comments made in the Office Action that clearly distinguish the presently pending claims over the cited prior art. Hence, it is respectfully requested that the amendment be entered.

This amendment could not have been made earlier as the amendment further defines the claims over the prior art in accordance with the suggestion made in the

Office Action, the suggestion first being made in the outstanding Office Action. Hence, since there remain no further issues to be resolved, it is respectfully requested that the present amendment be entered.

In conclusion, it is respectfully requested that the present amendment be entered in order to place the application in condition for allowance, which allowance is respectfully requested.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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Connie Herty